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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6,9,10,16 and 94-98* is/are pending in the application.

4a) Of the above claim(s) *94,95 and 97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6,9,10,16,96 and 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/15/2008 has been entered.

Election/Restrictions

The previous Action acknowledged Applicant's election with traverse of Group IV, claim(s) 4-6, 9, 10, 16, 19, 96, and 98, drawn to a method for the treatment of an eye disorder comprising administering a therapeutically effective amount of a dsRNA and detecting a product of the target gene of said dsRNA.

Status

Applicant's amendment to the claims filed 10/15/2008 is acknowledged. With entry of the amendment, claims 1, 4-6, 9, 10, 16, and 94-98 are pending. Claims 94, 95, and 97 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1, 4-6, 9, 10, 16, 96, and 98 are examined herein.

Applicant's response filed 10/15/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 7/15/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only

rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Domestic and Foreign Priority

The previous Action explained that written description support is not found in either of the domestic or foreign priority documents for the claimed invention. In particular written description and/or enabling support is not found in Provisional Application 60/431172 or Foreign Priority Application EP02008761.5 for a method of treating RPE, neurosensory retina, choroid, AMD, or diabetic retinopathy by administration of dsRNAs. Further, no support is found in either of the prior filed applications for interfering dsRNAs targeting SEQ ID NO:3, or for methods of treatment further comprising detecting the product of the target gene.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, with entry of the amendment filed 10/15/2008, the disclosure of the prior-filed application, Application No. 60/431,173 and EP 02008761.5 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for claims 1, 4-6, 9, 10, 16, 96, and 98.

Thus, for purposes of this examination, the earliest effective filing date of claims 1, 4-6, 9, 10, 16, 96, and 98 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Claim Objections

Claim 1 is objected to because of the recitation "inhibiting by RNA interference inside the eye." The recitation is somewhat awkward inasmuch as there is no object for the gerund "inhibiting." That is, the claim does not explain what exactly the composition is inhibiting. It is respectfully suggested Applicant include "the mRNA" or "said mRNA" after "inhibiting" to clarify the claim.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 and 10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

With entry of the amendment filed 10/15/2008, the claims are now drawn to methods of treating disorders of the eye related to angiogenesis, neovascularization, retinal pigment epithelium (RPE), neurosensory retina, choroid, or any combination thereof, wet-age macular degeneration, and diabetic retinopathy, comprising administering an interfering RNA complementary to SEQ ID NO:3.

The specification teaches and the extrinsic literature confirms that SEQ ID NO:3, a 3231-nucleotide DNA, corresponds to human phosphodiesterase 6B, cGMP-specific, rod, beta (PDE6B) mRNA (accession No. NM_000283). The specification teaches and the extrinsic evidence confirms that malfunction of this gene, and more specifically, missense or nonsense mutations in this gene are associated with autosomal recessive retinitis pigmentosa, or congenital stationary night blindness 3 (CSNB3).

Apart from this disclosure, however, neither the specification nor the prior or post-filing art teaches or suggests any link between the abnormal expression of PDE6B (SEQ ID NO:3) and any other eye disease. There is no evidence in the prior art or the specification of any correlation between the aberrant expression PDE6B and any of the disorders recited in claims 4, 5, 6, or 10, summarized above.

A review of the specification, or for that matter the prior art, fails to find a single working example showing or adequately representing that inhibiting the expression of an mRNA encoding wild-type or mutant PDE6B (SEQ ID NO:3) produces an effect correlative of treatment in any animal suffering from a disorder of the eye related to angiogenesis, neovascularization, retinal pigment epithelium (RPE), neurosensory retina, choroid, or any combination thereof, wet-age macular degeneration, and diabetic retinopathy. Neither the prior art nor the specification establishes any nexus between the inhibition of SEQ ID NO:3 and the treatment of each of these diseases. Accordingly, it is reasonable to question the objective truth of the assertions in the claims that the administration of an interfering dsRNA targeting SEQ ID NO:3 may be used to treat each of the disorders recited therein. With no examples to draw on and no direction or guidance of any kind in the specification showing how or even whether inhibition of SEQ ID NO:3 or any isoform thereof may be used to treat each of these disorders one of skill would necessarily need to resort to *de novo*, trial and error experimentation to achieve the claimed effects, and with no assurance of ever reaching a successful conclusion. The effects promised by the claims represent hoped-for functions---a starting point for further research, but nothing more. Such research, in the absence of any direction, guidance, or assurance by the specification, is considered to be undue.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Amending claim 10 to remove the clause "involved in angiogenesis and/or neovascularization" would be remedial insofar as claim 10. However, the amendment removing the clause would render the claim subject to the obviousness rejection below.

Claim Rejections - 35 USC § 103

Claims 1, 9, 16, 96, and 98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620) in view of:

1. Dryja et al. (US Patent 5,498,521);
2. Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268;
3. Collins et al. (1992) "The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain" *Genomics* 13 (3): 698-704;
4. Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33;
5. Tuschl et al. (US Patent Application 2004/0259247 A1); and
6. Bass (2001) *Nature* 411:428-9;
7. Tolentino et al. (US Patent 7,148,342); and
8. Pardridge (US 2002/0054902 A1).

Claim interpretation:

Apart from claim 98, the claims embrace all routes of administration, including retinal injection.

The rejection:

Robinson et al. taught methods for delivering antisense oligonucleotides intraocular to cells in the eye to treat diseases associated with the eye, including diabetic retinopathy and macular degeneration (pp. 1-18). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5), and combined with a variety of pharmaceutically acceptable carriers for intraocular, intravitreal, or systemic administration (column 10, lines 20-40; column 11, lines 5-15). For example, Robinson et al. taught that "Intravitreal injections of oligonucleotides against VEGF can be an effective means of inhibiting retinal neovascularization in an acute situation. However for long term therapy over a period of years, systemic delivery (intraperitoneal, intramuscular, subcutaneous, intravenous) either with carriers such as saline, slow release polymers, or liposomes should be considered" (column 11). Similarly at columns 9 and 10, Robinson et al. taught that the synthetic oligonucleotide could be administered by intraocular, oral ingestion, inhalation, or cutaneous, subcutaneous, intramuscular, or intravenous injection.

Thus, Robinson taught and suggested using therapeutic oligonucleotides such as antisense oligonucleotides to treat eye disease, and specifically recommended and showed that said therapeutic oligonucleotides may be delivered by virtually any known route including systemic administration and intraocular injection.

While Robinson et al. taught methods and materials making and using antisense oligonucleotides to treat eye diseases, Robinson et al. do not teach siRNAs targeted to SEQ ID NO:3.

Nevertheless, the mRNA sequence corresponding to SEQ ID NO:3 and its correlation with at least one eye disorder was known in the prior art.

Weber et al. taught the full length sequence of human rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283. Weber et al. further taught a link between rod cGMP phosphodiesterase and retinal disease, stating at page 6264 that the gene encoding the β-subunit of the rod cGMP phosphodiesterase is responsible for autosomal recessive retinal degeneration in the rd mouse.

Collins et al. echos and reinforces Weber et al., teaching the full length cDNA sequence of rod cGMP phosphodiesterase, which is found to be 100% identical to instant SEQ ID NO:3. Collins et al. state that the molecular cloning of the cDNA encoding for the PDEB represents the first step in establishing whether this gene plays a causative role in any one of the several human hereditary retinopathies.

Dryja et al. supplement Weber et al., teaching that the protein encoded by SEQ ID NO:3 is associated with a disorder of the eye. At column 1, Dryja et al. taught that mutant photoreceptor proteins such as cGMP phosphodiesterase may be involved in hereditary retinal degenerative diseases.In an exemplary embodiment, Dryja et al. show antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase corresponding to the gene disclosed by Weber et al. (see Example 9, column 15, lines 35-45). It was found that patients with mutations in the PDE .beta. gene had clinical

findings typical of retinitis pigmentosa (column 17, top). With regard to new claim 96, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase.

Epstein et al. taught antisense oligonucleotides for inhibiting phosphodiesterase genes, both *in vitro* and *in vivo*. Epstein et al. teach that antisense oligos can be used to inhibit essentially any isoform of PDE (page 21). Epstein et al. provide a complete blueprint for the design and preparation of antisense oligonucleotides against the known PDE gene sequences (see pages 22-25). Epstein et al. state that a number of excellent reviews have been written recently that describe the characteristics of the different PDE isoforms, their regulation, function, and progress in development of pharmacological inhibitors of PDE as therapeutic agents (page 21, 2nd column).

Tuschl et al. taught the methods and materials for making and using short double-stranded interfering RNA molecules (siRNAs) for inhibiting the expression of virtually any known mammalian gene in cells in vitro and in vivo for research and therapeutic purposes (pp. 1-16). It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179). In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene. The reference contains detailed descriptions and several examples typifying

the use of siRNA in cell culture, and the Application Publication expressly suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al. state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Tolentino et al. taught methods and materials for making and using short interfering RNAs to inhibit the expression of genes in the eye to treat diseases of the eye (cols. 1-20). It is said and shown that the siRNA may be administered systemically or intravenously, or by subretinal injection (cols. 12 and 16, and see Examples).

Pardridge taught immunoliposomes for delivering therapeutic genes across the blood brain barrier into cells in the eye for the treatment of ocular diseases, And showed that it is possible to obtain expression of an exogenous gene throughout the retina following intravenous injection of a non-viral preparation (cols. 1-18).

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to make and use siRNAs, as taught by Tuschl et al. and Bass, targeted to SEQ ID NO:3, corresponding to beta subunit of rod cGMP phosphodiesterase, to inhibit the expression of mutant isoforms of SEQ ID NO:3 and consequent development of ocular diseases associated with the expression mutant isoforms of SEQ ID NO:3, such as retinitis, as taught by the prior art cited herein. Further, it would have been obvious to administer said siRNAs by any number of means including systemic, as taught by Robinson et al. It would further have been obvious to apply the siRNAs directly to the area affected by the disease—the eye—by direct application, injection, or topically, as by eye drops. There is nothing in the art nor any evidence of record showing any express teaching away from the use of eye drops for the administration of any oligonucleotide-based therapeutic. It is a matter of common sense to apply the therapeutic agent directly to the area of treatment.

One would have been both well motivated and have had a reasonable expectation of success given the prior art taught that mutant isoforms of beta rod cGMP phosphodiesterase (i.e., SEQ ID NO:3) may predispose individuals to a form of retinal degeneration, given that Robinson et al. teach that antisense compounds may be used effectively in retinal cells specifically to inhibit the expression of genes associated retinal degeneration, and given that Epstein teaches that antisense compounds may be used effectively to inhibit the expression of phosphodiesterases in particular, and given that the level of skill in the art of delivery of therapeutic nucleic acids into the eyes of an animal was high at the time of invention, as evidenced by the prior art cited herein. Given that Tuschl et al. and Bass teach that siRNAs are in general more potent than antisense oligonucleotides for reducing gene expression in cells, one of skill would have been

motivated to substitute siRNAs for antisense oligonucleotides in the methods of Dryja et al. and/or Epstein et al. to silence the expression of genes such as SEQ ID NO:3 associated with eye disorders.

One would have had a reasonable expectation of success in targeting mutant forms of SEQ ID NO:3 as well as SEQ ID NO:3 itself given that Dryja et al. in combination with Weber et al. and Collins et al. taught both the wild type form, as disclosed in Weber et al., and common mutations thereof leading to eye-related disease (see example 9).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 10/15/2008 traversing the instant rejection under 35 USC 103 have been fully considered but are not persuasive.

Applicants argues the rejection should be withdrawn because antisense oligonucleotides and siRNAs were not art-recognized equivalents; therefore prior art teaching the use of antisense oligonucleotides to treat eye disease is not relevant to the suggestion to use siRNA to do the same. This argument is not persuasive because the art clearly taught that antisense oligonucleotides and short interfering RNAs may each be used to inhibit gene expression, albeit by different mechanisms and with different relative potencies. Tuschl et al. and Bass each directly compare and contrast the two technologies, which is direct evidence that the prior art recognized this functional equivalence. siRNAs and antisense oligonucleotides were each known to be useful for inhibiting the expression of a gene in vitro and in vivo. siRNAs were discovered

several years after antisense oligonucleotides, and simply represented at the time what was recognized to be a superior alternative to conventional antisense oligonucleotides.

Applicant further argues the prior art teaching antisense oligonucleotides for treatment of eye disease is not relevant to the instant methods using siRNA because the route of delivery is of critical importance, and the prior art suggests a low expectation of success in delivering siRNA across the blood brain barrier. This argument is not persuasive because 1) apart from claim 96, the claims require no particular means of delivery, and the prior art related to the use of therapeutic nucleic acids to treat eye disease recommends and shows delivery of oligonucleotides into the eye using multiple routes of delivery, including but not limited to systemic delivery across the blood brain barrier; 2) because the prior art neither discourages, discredits, nor dissuades one of skill from pursuing the use of siRNA in vivo to treat eye diseases of any kind by any delivery means; and 3) the level of skill in the art of nucleic acid delivery to cells in the eye in vivo was high at the time of invention, as shown by the prior art cited herein. The claims, then, do not distinguish the method in any way over that expressly recommended by the prior art.

Applicant has used routine methods to confirm what was already believed to be true: siRNA may be effectively delivered into cells in the eye in amounts sufficient to inhibit the expression of a gene in the eye. Indeed, Applicant shows no more than this in the specification. Thus, Applicant themselves show no treatment effects, but merely confirm at page 53 that eGFP expression in the eye may be reduced by systemic administration of siRNA.

Scientific confirmation of what was already reasonably believed to be true may be a valuable contribution but it does not give rise to a patentable invention (*PharmaStem Therapeutics Inc. v. ViaCell Inc.*, 83 USPQ2d 1289 (Fed. Cir. 2007). In the instant case,

Applicant has applied conventional techniques, known in the art for delivering nucleic acids into the eye to siRNA, and simply confirmed that, indeed, siRNA may be delivered into the eye. Again, the claims require no particular conditions, steps, or materials not already taught and suggested by the prior art. There is sufficient evidence to suggest one of skill in the art would have reasonably suspected that, using the proper delivery vehicle, siRNA may be effectively delivered into the cells in the eye either by direct or local administration or by systemic infusion, and many methods were known or recommended at the time for delivering therapeutic nucleic acids across the blood brain barrier.

Applicant cites US 2008/0213185 as evidence of the low expectation of success at the time of invention; however, Applicant appear to be mixing the standards for enablement with that required for obviousness. Absolute predictability is not required in either case, but only the reasonable expectation of success. The claims do not require prevention or cure, but simply treatment: any positive effect. Therefore Applicant's results are not "surprising" because they simply verify what the prior art suggested doing.

In sum, Applicant's arguments concerning delivery across the BBB, currently, are germane only to claim 96, as the other claims embrace all modes of delivery including intraocular injection. Moreover, the prior art taught all manners of delivery, providing one of skill with the guidance and direction needed to practice methods of the type now claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
December 1, 2008